AP&T Alimentary Pharmacology and Therapeutics

Comparative effectiveness of ledipasvir/sofosbuvir ± ribavirin vs. ombitasvir/paritaprevir/ritonavir + dasabuvir ± ribavirin in 6961 genotype 1 patients treated in routine medical practice

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Publication data
Submitted 9 April 2016
First decision 3 May 2016
Resubmitted 11 May 2016
Accepted 21 May 2016

This article was accepted for publication after full peer-review.

SUMMARY

Background
Real-world data are needed to inform hepatitis C virus (HCV) treatment decisions.

Aim
To assess the comparative effectiveness of ledipasvir/sofosbuvir ± ribavirin (LDV/SOF ± RBV) vs. ombitasvir/paritaprevir/ritonavir + dasabuvir (OPrD) ± RBV in genotype 1 HCV patients treated in routine medical practice.

Methods
Observational intent-to-treat cohort of genotype 1 patients initiating 8 or 12 weeks of LDV/SOF ± RBV or 12 weeks of OPrD ± RBV. Sustained virological response (SVR) required RNA below the limit of quantification at least 10 weeks after end of treatment.

Results
6961 patients initiated LDV/SOF ($N = 4478$), LDV/SOF + RBV ($N = 1269$), OPrD ($N = 297$), and OPrD + RBV ($N = 917$) at 126 facilities. Intention-to-treat SVR rates were 91.4% (3813/4170) for LDV/SOF, 90.0% (1098/1220) for LDV/SOF + RBV, 95.1% (269/283) for OPrD and 85.8% (746/869) for OPrD + RBV. SVR rates in those completing 8 weeks of LDV/SOF were 91.7% (1223/1333) and 12 weeks of LDV/SOF 94.6% (2475/2615), LDV/SOF + RBV 92.2% (1033/1120), OPrD 98.0% (248/253) and OPrD + RBV 95.5% (705/738). Significant predictors of SVR were African American race (OR 0.71, 95%CI 0.59–0.86, $P < 0.001$), body mass index (BMI) > 30 kg/m^2 (OR 0.73, 95% CI 0.60–0.89, $P = 0.002$), FIB4 > 3.25 (OR 0.60, 95% CI 0.49–0.72, $P < 0.001$), OPrD + RBV compared to LDV/SOF (OR 0.60, 95% CI 0.48–0.76, $P < 0.001$) and subtype 1b (OR 1.38, 95% CI 1.11–1.71, $P = 0.003$). For those completing 12 weeks, FIB-4 > 3.25 and high BMI remained significant predictors.

Conclusions
In this robust real-world cohort, SVR rates were similar to clinical trials. FIB-4 > 3.25 and high BMI were significant negative predictors of SVR. Reduced odds of SVR in African Americans and with OPrD + RBV likely arose from excess early discontinuation as these factors were no longer significant, when limited to patients completing a 12-week course.

doi:10.1111/apt.13696

INTRODUCTION

The landscape of antiviral therapy for chronic hepatitis C virus (HCV) infection continues to advance as all-oral options expand. Sustained virological response (SVR) rates reported in clinical trials with all-oral regimens are consistently above 90% for most HCV-infected patient populations and have become the expected norm. Because of the rapidity with which HCV therapies are progressing and the absence of comparative clinical trials, providers are left to extrapolate information to make clinical decisions about medication selection. Emerging real-world data of individual therapies have demonstrated results comparable to registration trials, however, comparative effectiveness evaluations are needed to determine whether clinical differences exist between regimens.[1–6] Comparative effectiveness analyses will become increasingly important as patients, providers, healthcare systems and managed care organisations consider additional nuances of convenience, drug interactions, treatment duration and ultimately cost effectiveness.

Ledipasvir/sofosbuvir (LDV/SOF) and ombitasvir/paritaprevir/ritonavir plus dasabuvir (OPrD) have been extensively evaluated individually in clinical trials of HCV-infected adults. The SVR rates in LDV/SOF trials of genotype 1 patients with and without cirrhosis ranged from 94% to 99% and in OPrD trials SVR rates ranged from 89% to 99%.[7–14] While these outcomes appear similar, differences in study design and patient populations prevent direct cross-study comparison of results.

Hepatitis C virus disproportionally affects the veteran population and the Department of Veterans Affairs (VA) is the largest US provider of healthcare to HCV-infected individuals caring for nearly 5% of all individuals in the US with HCV infection.[15, 16] Thus, ongoing evaluation of the effectiveness of HCV antiviral regimens remains a priority for VA.[17] With the rapid uptake of all-oral HCV regimens across the VA system and the diverse HCV-infected veteran population receiving these regimens, we examined SVR rates and comparative effectiveness of LDV/SOF ± ribavirin (RBV) vs. OPrD ± RBV in genotype 1 HCV-infected veterans treated in routine medical practice.

MATERIALS AND METHODS

This was an observational intent-to-treat cohort analysis of HCV-infected veterans receiving LDV/SOF ± RBV or OPrD ± RBV from VA. Data for this study were obtained from the VA's national Clinical Case Registry for HCV, an extract of the VA electronic medical record that contains demographics, laboratory results, pharmacy information and International Classification of Diseases diagnosis codes from inpatient hospitalisations, outpatient visits and problem lists of HCV-infected veterans seen at all VA medical facilities.[18]

Eligible subjects included all genotype 1 HCV-infected veterans from any VA facility nationwide who initiated 8 or 12 weeks of VA-prescribed LDV/SOF ± RBV or 12 weeks of OPrD ± RBV by 31 March 2015 with an end of treatment (EOT) by 14 July 2015 and a days supply less than or equal to 91 days. For patients who received multiple courses of therapy, only the first course was included. The choice of regimen and timing of follow-up visits and laboratory testing was at the discretion of the provider as patients were treated in routine practice. The present cohort includes 4356 treatment naïve patients treated with LDV/SOF ± RBV who were reported on previously.[19] Patients were excluded if they changed regimens without a treatment interruption (n = 64), had a baseline HCV RNA ≤1000 IU/mL (n = 218), had a liver transplant (n = 141), or had genotype subtype 1a and received OPrD without RBV (n = 16).

Treatment outcome

Patients were considered to have SVR if they had HCV RNA results below the limit of quantification on all HCV RNA tests after the EOT including at least one test 10 weeks or more after the EOT. The 10 week time point was chosen to account for variability of clinic visits and of laboratory testing draws in clinical practice. Patients were categorised as not achieving SVR if they had a HCV RNA above the limit of quantification after the EOT, had no HCV RNA testing after the EOT and a HCV RNA above the limit of quantification on their last HCV RNA test while on treatment or died while on treatment or within 10 weeks of the EOT. Patients with HCV RNA below the limit of quantification on their last HCV viral load test, either on treatment or after the EOT, but no test 10 weeks of more after the EOT were excluded from the SVR analysis. The EOT was calculated as the last day covered by prescriptions of LDV/SOF or OPrD using the dates the medication was dispensed and the days' supply. HCV RNA was categorised as above or below the lower limit of quantification based on the locally reported HCV RNA result of which 98% utilised assays with a lower limit of quantification of 15 U/mL or less. Patients were followed from the initiation of LDV/SOF ± RBV or OPrD ± RBV through 29 February 2016, allowing for more than 32 weeks of follow-up after the EOT for all patients in the cohort.

Control variables

Demographic and other baseline variables were determined at the time of treatment initiation and included age, gender, race/ethnicity, diabetes, HIV coinfection, history of decompensated liver disease (defined by oesophageal variceal haemorrhage, hepatic coma, hepatorenal syndrome or spontaneous bacterial peritonitis), prescribed proton pump inhibitor use, prior HCV antiviral treatment experience and HCV genotype 1 subtype. Subtype 1a included patients with reported results of 1a, mixed 1a/1b or 1 with subtype unspecified. Prior virological response was based on the most recent VA course of HCV antiviral treatment and categorised as relapse, partial response, null response and not defined. Baseline values for height and weight used to calculate body mass index (BMI) and the laboratory tests for alanine aminotransferase, aspartate aminotransferase, platelets and baseline HCV RNA were defined as the value within 1 year before and closest to the treatment start date. A FIB-4 score >3.25 at the start of treatment using baseline laboratory values was used as a marker of advanced liver disease.[20, 21] Patients with FIB-4 ≤ 3.25 were considered to be 'noncirrhotic'.

In VA, HCV antiviral prescriptions are frequently filled for quantities less than 28 days. Patients were considered to have completed 8 weeks of LDV/SOF if they had received between 49 and 63 days' worth of medication and 12 weeks LDV/SOF ± RBV or OPrD ± RBV if they received between 77 and 91 days' worth of medication.

Statistical analysis

Univariate comparisons used the Pearson chi-squared test with Yates' continuity correction for categorical variables. Multivariate logistic regression models were constructed to model SVR. Models included age, gender, race/ethnicity, diabetes, history of decompensated liver disease, treatment experience, BMI, FIB-4, genotype 1 subtype, and regimen. In a sensitivity analysis proton pump inhibitor use was included in the model. A set of models with the above baseline variables was constructed with all patients and with only patients who completed 12 weeks of treatment.

For all comparisons, a $P < 0.01$ was considered statistically significant. All analyses were performed using R version 3.1 (R Foundation for Statistical Computing, Vienna, Austria).

The protocol was approved by the Stanford University Institutional Review Board and the VA Palo Alto Health Care System Research and Development Committee.

RESULTS

In total, 6961 patients with HCV genotype 1 initiated LDV/SOF ± RBV ($n = 5747$) or OPrD ± RBV ($n = 1214$) at 126 VA facilities. The mean age for the cohort was 61.4 years, 96.3% were male, 36.0% were African-American, 31.5% had diabetes, 3.2% had a history of decompensated liver disease, 23.6% were treatment experienced, 35.4% had a BMI ≥30 kg/m^2, and 29.5% had a FIB-4 > 3.25.

Baseline characteristics for the cohort by regimen appear in Table 1. For the cohort, 64.3% ($n = 4478$) received LDV/SOF, 18.2% ($n = 1269$) received LDV/SOF + RBV, 4.3% ($n = 297$) received OPrD and 13.2% ($n = 917$) received OPrD + RBV. Patients who received LDV/SOF+RBV were most likely to be treatment-experienced and to have markers of advanced liver disease including a history of decompensated liver disease, lower mean platelet count, higher mean FIB-4 score, and FIB-4 > 3.25.

Among patients who received LDV/SOF, 3.6% ($n = 159$) discontinued treatment before 8 weeks, 32.7% ($n = 1464$) received 8 weeks, 1.7% ($n = 77$) discontinued treatment between 8 and 12 weeks and 62.0% ($n = 2778$) received 12 weeks. In total, 94.7% completed either an 8 or 12 week course. Among people who received LDV/SOF + RBV, 8.1% (103/1269) discontinued treatment prior to completing 12 weeks. Among patients who received OPrD or OPrD+RBV, 11.4% (34/297) and 15.2% (140/917) of patients, respectively, discontinued treatment prior to completing a 12 week course. Significantly more patients receiving OPrD + RBV discontinued treatment prior to completing a 12-week course compared to those receiving LDV/SOF + RBV ($P < 0.001$).

Sustained virological response results were available for 94.0% ($n = 6542$) of patients in the cohort, including 24 patients who died while on treatment or shortly after who were categorised as no SVR. Four hundred nineteen patients whose last HCV RNA was undetectable, but occurred while still on treatment ($n = 123$) or less than 10 weeks after the EOT ($n = 296$), were excluded from the SVR analysis. Three hundred five patients had an undetectable HCV RNA obtained 10–11 weeks after the EOT and were included in the SVR analysis for reasons described previously.

Among 4170 LDV/SOF patients 91.4% achieved SVR; among 1220 LDV/SOF + RBV patients 90.0% achieved SVR; among 283 OPrD patients 95.1% achieved SVR and among 869 OPrD + RBV patients 85.8% achieved SVR (Table 2). For patients who received LDV/SOF, the SVR rates differed statistically based on categories of

Table 1 | Baseline characteristics and 4 week on-treatment response of genotype 1 patients receiving ledipasvir/sofosbuvir- or ombitasvir/paritaprevir/ritonavir plus dasabuvir-based regimens with durations of 12 weeks or less

	Genotype 1 cohort (*N* = 6961)	LDV/SOF (*N* = 4478)	LDV/SOF + RBV (*N* = 1269)	OPrD (*N* = 297)	OPrD + RBV (*N* = 917)
Age (years)	61.4 ± 6.2 (24.5–90.8)	61.2 ± 6.5 (25.3–90.8)	61.9 ± 5.2 (24.5–86.2)	62.3 ± 5.9 (28.5–77.2)	61.5 ± 6.0 (26.7–85.3)
Gender, male	96.3 (6703)	95.9 (4295)	97.2 (1233)	96.3 (286)	96.9 (889)
Race/ethnicity					
African-American	36.0 (2506)	38.2 (1712)	29.0 (368)	46.8 (139)	31.3 (287)
Caucasian	51.6 (3591)	50.5 (2263)	54.5 (692)	43.4 (129)	55.3 (507)
Hispanic	5.4 (376)	4.5 (304)	8.0 (102)	4.0 (12)	6.4 (59)
Other/multiple	7.0 (488)	6.7 (300)	8.4 (107)	5.7 (17)	7.0 (64)
Diabetes	31.5 (2195)	30.3 (1357)	37.7 (479)	33.3 (99)	28.4 (260)
Proton pump inhibitor	27.7 (1927)	26.3 (1178)	35.4 (449)	25.3 (75)	24.5 (225)
HIV coinfected	4.5 (310)	5.3 (237)	3.7 (47)	2.4 (7)	2.1 (19)
Decompensated liver disease	3.2 (224)	1.9 (87)	8.6 (109)	0.7 (2)	2.8 (26)
Any treatment experience	23.6 (1645)	16.0 (718)	53.0 (673)	19.2 (57)	21.5 (197)
DAA experience (% of treatment experienced)	44.1 (726)	39.1 (281)	62.4 (420)	7.0 (4)	10.7 (21)
Prior SOF + simeprevir (*n*)*	71	12	57	0	2
Prior SOF + PEG + RBV or SOF + RBV (*n*)*	131	29	96	0	6
Prior boceprevir (*n*)*	494	222	253	4	15
Prior telaprevir (*n*)*	74	21	53	0	0
Prior treatment response	*N* = 1645	*N* = 718	*N* = 673	*N* = 57	*N* = 197
Relapse	29.9 (492)	24.0 (172)	39.2 (264)	14.0 (8)	24.4 (48)
Partial	10.2 (167)	9.1 (65)	10.1 (68)	21.1 (12)	11.2 (22)
Null	11.3 (186)	9.6 (69)	11.1 (75)	12.3 (7)	17.8 (35)
Unknown	48.6 (800)	57.4 (412)	39.5 (266)	52.6 (30)	46.7 (92)
BMI (kg/m^2)	28.8 ± 5.3 (15.8–65.2)	28.5 ± 5.2 (15.8–65.2)	30.0 ± 5.5 (16.4–60.1)	28.2 ± 5.0 (16.0–53.7)	28.8 ± 5.3 (17.6–58.5)
BMI (kg/m^2)					
<25	23.1 (1605)	24.8 (1109)	17.9 (227)	24.2 (72)	21.5 (197)
25–29	41.6 (2893)	41.6 (1863)	37.6 (477)	49.8 (148)	44.2 (405)
≥30	35.4 (2463)	33.6 (1506)	44.5 (565)	25.9 (77)	34.4 (315)
ALT (U/L)	74.1 ± 56.5 (8–659)	71.4 ± 55.9 (8–659)	80.3 ± 52.3 (13–445)	62.6 ± 50.7 (13–552)	82.4 ± 64.3 (11–560)
AST (U/L)	64.4 ± 45.5 (6–614)	60.5 ± 43 (6–614)	76.6 ± 48.2 (11–503)	50.6 ± 34.8 (14–322)	70.4 ± 52.1 (13–499)
Platelets (K/μL)	185.6 ± 69.9 (6–759)	194.4 ± 68.2 (6–661)	150.3 ± 67.9 (22–759)	214.6 ± 59.6 (81–421)	181.8 ± 66.7 (32–470)
FIB-4	3.2 ± 3.7 (0.1–185.0)	2.8 ± 3.8 (0.1–185.0)	4.7 ± 4.1 (0.5–34.7)	2.0 ± 1.2 (0.3–10.0)	3.3 ± 2.9 (0.4–27.3)
FIB-4	*N* = 6936	*N* = 4460	*N* = 1267	*N* = 296	*N* = 913
≤3.25	70.5 (4889)	76.4 (3406)	47.8 (605)	89.5 (265)	67.1 (613)
>3.25	29.5 (2047)	23.6 (1054)	52.2 (662)	10.5 (31)	32.9 (300)
HCV RNA (log IU/mL)	6.2 ± 0.7 (3.0–7.9)	6.2 ± 0.7 (3.1–7.9)	6.2 ± 0.7 (3.0–7.8)	6.3 ± 0.6 (3.9–7.6)	6.3 ± 0.7 (3.0–7.8)
HCV RNA (IU/mL)					
<6 000 000	82.0 (5705)	82.7 (3705)	84.6 (1073)	76.8 (228)	76.2 (699)
≥6 000 000	18.0 (1256)	17.3 (773)	15.4 (196)	23.2 (69)	23.8 (218)
HCV subtype 1b	27.3 (1897)	24.2 (1085)	23.4 (297)	100.0 (297)	23.8 (218)

Table 1 | (Continued)

	Genotype 1 cohort (N = 6961)	LDV/SOF (N = 4478)	LDV/SOF + RBV (N = 1269)	OPrD (N = 297)	OPrD + RBV (N = 917)
IL28B polymorphism	N = 989	N = 598	N = 204	N = 33	N = 154
CC	20.3 (201)	22.6 (135)	15.2 (31)	9.1 (3)	20.8 (32)
CT	54.0 (534)	52.7 (315)	58.3 (119)	51.5 (17)	53.9 (83)
TT	25.7 (254)	24.7 (148)	26.5 (54)	39.4 (13)	25.3 (39)

Continuous variables reported as mean ± s.d. (range). Categorical variables reported as % (n).

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DAA, direct-acting antiviral; LDV/SOF, ledipasvir/sofosbuvir; OPrD, ombitasvir/paritaprevir/ritonavir + dasabuvir; PEG, pegylated interferon; SOF, sofosbuvir; RBV, ribavirin.

* Some patients received more than one prior DAA regimen and are included in the count for each regimen they received.

race/ethnicity, BMI, and FIB-4. For patients who received LDV/SOF + RBV, the SVR rates differed statistically based on proton pump inhibitor use and FIB-4. No statistically significant differences in SVR were observed according to baseline patient characteristics among patients receiving either OPrD or OPrD + RBV, and responses were generally similar to that observed in the overall population. SVR data for treatment naïve and experienced patients by subgroup can be found in Table S1A and B.

For patients who completed an 8 week course of LDV/SOF or a 12 week course of LDV/SOF ± RBV or OPrD ± RBV, SVR rates were consistently higher overall and among subgroups when compared to the intention-to-treat SVR rates (Table 3). With regard to the impact of treatment duration among patients who received LDV/SOF, the SVR rate in those who received 8 weeks was 91.7% (1223/1333) and 94.6% (2475/2615) in those who received 12 weeks. An SVR rate of 92.2% (1033/1120) was achieved in patients completing 12 weeks of LDV/SOF + RBV and 95.5% (705/738) in those completing 12 weeks of OPrD+RBV. In genotype 1b patients who received 12 weeks of OPrD, an SVR rate of 98.0% (248/253) was achieved. In 1098 patients who met the Food and Drug Administration (FDA) labelling considerations for a shortened LDV/SOF course consisting of treatment-naïve, without cirrhosis (defined as FIB-4 ≤ 3.25), and a baseline HCV RNA <6 000 000 IU/mL and who completed 8 weeks of LDV/SOF therapy, the SVR rate was 93.2% (1023/1098). In 905 patients who also met the FDA considerations for a shortened LDV/SOF course but nevertheless received 12 weeks of LDV/SOF therapy, the SVR rate was 96.6% (874/905) (P = 0.001 compared to 8 week course).

In multivariate analysis, significant independent predictors of decreased odds of SVR were African American race (OR 0.71, 95% CI 0.59–0.86, $P < 0.001$), BMI ≥30 kg/m^2 (OR 0.73, 95% CI 0.60–0.89, P = 0.002), FIB-4 > 3.25 (OR 0.60, 95% CI 0.49–0.72, $P < 0.001$) and use of OPrD + RBV compared to LDV/SOF (OR 0.60, 95% CI 0.48–0.76, $P < 0.001$) (Table 4). Genotype subtype 1b was an independent predictor of increased odds of SVR (OR 1.38, 95% CI 1.11–1.71, P = 0.003). Age, gender, diabetes, history of decompensated liver disease and treatment experience did not predict SVR. In the sensitivity analysis proton pump inhibitor use was not associated with a difference in the odds of achieving SVR (0.85, 95% CI 0.71–1.03, P = 0.09). In models limited to patients receiving 12 weeks of treatment, only BMI ≥30 kg/m^2 (OR 0.66, 95% CI 0.49–0.88, P = 0.004) and FIB4 > 3.25 remained significant (OR 0.46, 95% CI 0.35–0.60, $P < 0.001$).

DISCUSSION

In this robust comparative effectiveness analysis of LDV/SOF ± RBV vs. OPrD ± RBV in genotype 1 HCV-infected veterans treated in routine medical practice, high SVR rates were achieved overall (86–95%) and within subgroups (83–100%). In multivariate models, OPrD + RBV was found to be less effective than LDV/SOF and patients receiving the former were 40% less likely to achieve SVR. However, in patients who completed a 12-week treatment course there was no difference in effectiveness. Similar to clinical trials, curative all-oral treatment has become a reality for over 90% of patients treated in the real-world, even in those with characteristics previously associated with poorer outcomes. This analysis demonstrates the real-world

Table 2 | SVR rates by regimen for genotype 1 patients receiving ledipasvir/sofosbuvir- or ombitasvir/paritaprevir/ritonavir plus dasabuvir-based regimens with durations of 12 weeks or less

	LDV/SOF (*N* = 4170)	*P* value*	LDV/SOF+RBV (*N* = 1220)	*P* value*	OPrD (*N* = 283)	OPrD + RBV (*N* = 869)
Overall SVR	91.4 (3813/4170)		90.0 (1098/1220)		95.1 (269/283)	85.8 (746/869)
Age (years)						
<55	94.2 (420/446)		92.8 (77/83)		95.0 (19/20)	88.0 (66/75)
55–64	90.5 (2306/2547)		89.4 (706/790)		94.3 (148/157)	86.2 (487/565)
≥65	92.4 (1087/1177)		90.8 (315/347)		96.2 (102/106)	84.3 (193/229)
Gender						
Male	91.2 (3649/3999)		89.9 (1065/1184)		94.9 (258/272)	85.6 (721/842)
Female	95.9 (164/171)		91.7 (33/36)		100.0 (11/11)	92.6 (25/27)
Race/ethnicity						
African American	90.0 (1426/1584)	0.003	90.7 (320/353)		90.8 (118/130)	82.9 (228/275)
Caucasian	92.8 (1967/2119)		89.7 (594/662)		98.4 (123/125)	87.4 (418/478)
Hispanic	89.6 (172/192)		87.9 (87/99)		100.0 (11/11)	85.5 (47/55)
Other/multiple	90.2 (248/275)		91.5 (97/106)		100.0 (17/17)	86.9 (53/61)
Diabetes						
No	91.7 (2651/2892)		90.3 (691/765)		94.6 (176/186)	86.2 (532/617)
Yes	90.9 (1162/1278)		89.5 (407/455)		95.9 (93/97)	84.9 (214/252)
Proton pump inhibitor						
No	91.7 (2805/306)		91.9 (726/790)	0.004	95.3 (203/213)	85.7 (559/652)
Yes	90.8 (1008/1110)		86.5 (372/430)		94.3 (66/70)	86.2 (187/217)
HIV coinfection						
No	91.4 (3605/3944)		90.1 (1059/1175)		95.3 (263/276)	85.8 (730/851)
Yes	92.0 (208/226)		86.7 (39/45)		85.7 (6/7)	88.9 (16/18)
Decompensated liver disease						
No	91.5 (3745/4091)		90.4 (1010/1117)		95.0 (267/281)	86.6 (731/844)
Yes	86.1 (68/79)		85.4 (88/103)		100.0 (2/2)	60.0 (15/25)
Treatment experienced						
No	91.3 (3188/3492)		92.1 (522/567)		95.6 (218/228)	85.4 (580/679)
Yes	92.2 (625/678)		88.2 (576/653)		92.7 (51/55)	87.4 (166/190)
DAA-experienced (compared to all other treatment experienced)						
No	91.3 (377/413)		90.2 (222/246)		92.2 (47/51)	87.1 (149/171)
Yes	93.6 (248/265)		87.0 (354/407)		100.0 (4/4)	89.5 (17/19)
Prior treatment response						
Relapse	95.7 (156/163)		86.7 (221/255)		87.5 (7/8)	86.4 (38/44)
Partial	95.2 (59/62)		85.3 (58/68)		100.0 (12/12)	90.9 (20/22)
Null	86.6 (58/67)		90.4 (66/73)		85.7 (6/7)	91.4 (32/35)
Unknown	91.2 (352/386)		89.9 (231/257)		92.9 (26/28)	85.4 (76/89)
BMI (kg/m^2)						
<25	90.3 (931/1031)		91.0 (201/221)		94.2 (65/69)	84.9 (157/185)
25–29	93.1 (1613/1733)	0.005	91.4 (417/456)		96.4 (134/139)	86.5 (334/386)
≥30	90.3 (1269/1406)		88.4 (480/543)		93.3 (70/75)	85.6 (255/298)
FIB-4						
≤3.25	92.8 (2926/3154)	<0.001	92.5 (539/583)	0.008	95.3 (241/253)	87.1 (508/583)
>3.25	87.4 (879/1006)		87.7 (557/635)		93.1 (27/29)	84.0 (237/282)
HCV RNA (IU/mL)						
<6 000 000	91.4 (3148/3445)		89.6 (925/1032)		95.4 (207/217)	85.3 (563/660)
≥6 000 000	91.7 (665/725)		92.0 (173/188)		93.9 (62/66)	87.6 (183/209)
HCV subtype						
1a†	90.9 (2860/3146)		89.6 (840/938)		–	85.3 (563/660)
1b	93.1 (953/1024)		91.5 (258/282)		95.1 (269/283)	87.6 (183/209)

Table 2 | (Continued)

	LDV/SOF (*N* = 4170)	*P* value*	LDV/SOF+RBV (*N* = 1220)	*P* value*	OPrD (*N* = 283)	OPrD + RBV (*N* = 869)
IL28B polymorphism	*N* = 570		*N* = 200		*N* = 30	*N* = 147
CC	92.2 (119/129)		96.8 (30/31)		100.0 (3/3)	80.0 (24/30)
CT	92.3 (276/299)		92.2 (107/116)		93.8 (15/16)	85.2 (69/81)
TT	93.7 (133/142)		90.6 (48/53)		81.8 (9/11)	83.3 (30/36)

Categorical variables reported as % (*n*).

BMI, body mass index; DAA, direct-acting antiviral; LDV/SOF, ledipasvir/sofosbuvir; OPrD, ombitasvir/paritaprevir/ritonavir + dasabuvir; RBV, ribavirin; SVR, sustained virological response.

* *P* value listed for $P < 0.01$.

† Subtype 1a includes 1a, mixed 1a/1b and 1 with subtype unspecified.

comparative effectiveness of all-oral DAA regimens in individuals with genotype 1 HCV infection that clinicians, patients and payers have anticipated.

The current HCV treatment landscape remains complex despite increasingly more effective HCV regimens, with variability in outcomes for patients with previous treatment experience, genotype subtype, race, degree of underlying liver disease and other comorbid conditions.[7, 8, 13, 14, 22–24] Because of the large sample size in this cohort, we were able to do robust subgroup analyses to examine differences among these characteristics and identify where challenges remain.

Despite SVR rates higher than any previously reported among veterans with advanced liver disease, the presence of advanced liver disease as indicated by a FIB-4 score greater than 3.25 remained a significant negative predictor of response with an apparent impact for treatment naïve and treatment experienced patients and across all regimens.[5, 23, 25] Over 2000 patients with advanced liver disease were included in this cohort. In multivariate models, the presence of advanced liver disease predicted reduced odds of achieving SVR by 40% independent of treatment experience and regimen. Absolute SVR rates in treatment naïve patients were generally four to five percent lower in those with advanced liver disease compared to those without advanced liver disease for patients who received LDV/SOF (87.6% vs. 92.6%), who received LDV/SOF + RBV (90.0% vs. 94.7%), and who received OPrD (91.7% vs. 96.1%). Current AASLD/IDSA treatment guidelines and FDA labelling recommend LDV/SOF for 12 weeks in treatment naïve patients with cirrhosis based largely on data from 34 patients in the ION-1 trial.[7, 26, 27] However, our observation of SVR rate of 87.6% with LDV/SOF in 889 treatment naïve patients with FIB4 scores >3.25 indicate SVR rates with this regimen may be below the 90% bar for which all-oral regimen expectations have been set and other treatment options might need to be considered in such patients.

In treatment experienced patients with and without advanced liver disease, reductions of 5–8% in SVR rates were seen in patients who received LDV/SOF (85.5% vs. 93.5%), who received LDV/SOF + RBV (85.4% vs. 90.9%), and who received OPrD + RBV (82.1% vs. 89.6%). The reduced SVR rates in the low to mid-80s in treatment experienced patients with advanced liver disease in this study mirror the 86% and 82% SVR rates observed in ION-2 in treatment-experienced cirrhotic patients receiving 12 weeks of LDV/SOF and LDV/SOF + RBV respectively.[8] In the TURQUOISE-II study SVR rates were 87% and 95% in treatment experienced cirrhotic null responders treated for 12 and 24 weeks respectively with OPrD+RBV.[14] The large number of patients included in our study coupled with the similar results obtained from ION-2 and TURQUOISE-II suggest that lower SVR rates may be expected in cirrhotic patients and particularly treatment-experienced cirrhotic patients treated in routine clinical practice. Extended treatment of 24 weeks in such patients may be warranted to achieve higher SVR rates.

In this cohort, SVR data were available for over 2300 African Americans. Multivariate modelling indicated African American race was associated with a 29% reduction in the odds of SVR. This effect was observed in multivariate models of the overall cohort but not in models limited to patients completing a 12 week treatment course suggesting that the reduced odds of SVR for African Americans arose in large part from excess early treatment discontinuations and from diminished effectiveness of 8-week LDV/SOF in African Americans, which has also been observed in retrospective analyses of the ION clinical trials.[22] Numerically lower SVR rates

Table 3 | SVR rates by regimen for genotype 1 patients receiving ledipasvir/sofosbuvir- or ombitasvir/paritaprevir/ritonavir plus dasabuvir-based regimens who received 8 or 12 weeks of LDV/SOF and 12 weeks of all other regimens

	LDV/SOF (*N* = 1333), 8 weeks	LDV/SOF (*N* = 2615) 12 weeks	*P* value*	LDV/SOF+RBV (*N* = 1120), 12 weeks	*P* value*	OPrD (*N* = 253), 12 weeks	OPrD + RBV (*N* = 738), 12 weeks
Overall SVR	91.7 (1223/1333)	94.6 (2475/2615)		92.2 (1033/1120)		98.0 (248/253)	95.5 (705/738)
Age (years)							
<55	94.8 (164/173)	96.4 (244/253)		95.7 (67/70)		100.0 (18/18)	92.9 (65/70)
55–64	91.2 (730/800)	94.0 (1510/1606)		92.0 (669/727)		97.2 (139/143)	95.5 (463/485)
≥65	91.4 (329/360)	95.4 (721/756)		92.0 (297/323)		98.9 (91/92)	96.7 (177/183)
Gender							
Male	91.6 (1164/1271)	94.5 (2376/2515)		92.2 (1001/1086)		97.9 (238/243)	95.5 (681/713)
Female	95.2 (59/62)	99.0 (99/100)		94.1 (32/34)		100.0 (10/10)	96.0 (24/25)
Race/ethnicity							
African-American	89.5 (461/515)	94.3 (920/976)		93.7 (296/316)		96.5 (109/113)	94.3 (214/227)
Caucasian	93.5 (632/676)	95.4 (1278/1339)		91.4 (562/615)		99.1 (111/112)	95.2 (395/415)
Hispanic	91.7 (44/48)	94.0 (126/134)		91.8 (78/85)		100.0 (11/11)	100.0 (45/45)
Other/multiple	91.5 (86/94)	91.0 (151/166)		93.3 (97/104)		100.0 (17/17)	100.0 (51/51)
Diabetes							
No	92.5 (910/984)	94.8 (1657/1748)		92.5 (650/703)		97.0 (164/169)	95.3 (502/527)
Yes	89.7 (313/349)	94.3 (818/867)		91.8 (383/417)		100.0 (84/84)	96.2 (203/211)
Proton pump inhibitor							
No	91.8 (944/1028)	94.9 (1780/1875)		94.3 (679/720)	<0.001	97.4 (187/192)	95.1 (528/555)
Yes	91.5 (279/305)	93.9 (695/740)		88.5 (354/400)		100.0 (61/61)	96.7 (177/183)
HIV coinfection							
No	91.6 (1193/1302)	94.6 (2302/2434)		92.3 (995/1078)		98.4 (242/246)	95.4 (690/723)
Yes	96.8 (30/31)	95.6 (173/181)		90.5 (38/42)		85.7 (6/7)	100.0 (15/15)
Decompensated liver disease							
No	91.8 (1219/1328)	94.8 (2414/2547)		92.3 (947/1026)		98.0 (246/251)	95.7 (691/722)
Yes	80.0 (4/5)	89.7 (61/68)		91.5 (86/94)		100.0 (2/2)	87.5 (14/16)
Treatment experienced							
No	92.1 (1168/1268)	94.3 (1922/2038)		94.1 (482/512)		97.5 (199/204)	95.2 (550/578)
Yes	84.6 (55/65)	95.8 (553/577)		90.6 (551/608)		100.0 (49/49)	96.9 (155/160)
DAA-experienced (compared to all other treatment experienced)							
No	83.3 (40/48)	94.8 (327/345)		92.2 (214/232)		100.0 (45/45)	96.5 (139/144)
Yes	88.2 (15/17)	97.4 (226/232)		89.6 (337/376)		100.0 (4/4)	100.0 (16/16)
Prior treatment response							
Relapse	83.3 (5/6)	98.7 (148/150)		90.1 (210/233)		100.0 (7/7)	100.0 (36/36)
Partial	66.7 (2/3)	96.5 (55/57)		84.8 (56/66)		100.0 (11/11)	100.0 (20/20)
Null	100.0 (5/5)	87.9 (51/58)		89.9 (62/69)		100.0 (6/6)	93.3 (28/30)
Unknown	84.3 (43/51)	95.8 (299/312)		92.9 (223/240)		100.0 (25/25)	95.9 (71/74)
BMI (kg/m^2)							
<25	90.7 (330/364)	95.1 (564/593)		94.0 (187/199)		98.4 (61/62)	96.1 (149/155)
25–29	93.7 (503/537)	95.4 (1061/1112)		93.2 (398/427)		98.4 (123/125)	96.6 (314/325)
≥30	90.3 (390/432)	93.4 (850/910)		90.7 (448/494)		97.0 (64/66)	93.8 (242/258)
FIB-4							
≤3.25	92.2 (1087/1179)	96.3 (1750/1817)	<0.001	94.8 (507/535)	0.003	98.7 (223/226)	95.0 (475/500)
>3.25	88.6 (132/149)	90.8 (721/794)		89.9 (525/584)		92.3 (24/26)	96.6 (230/238)
HCV RNA (IU/mL)							
<6 000 000	92.4 (1187/1285)	94.6 (1860/1967)		92.0 (867/942)		97.4 (189/194)	96.0 (534/556)
≥6 000 000	75.0 (36/48)	94.9 (615/648)		93.3 (166/178)		100.0 (59/59)	94.0 (171/182)
HCV subtype							
1a†	91.0 (881/968)	94.4 (1904/2018)		92.1 (792/860)		–	94.6 (527/557)
1b	93.7 (342/365)	95.6 (571/597)		92.7 (241/260)		98.0 (248/253)	98.3 (178/181)
IL28B Polymorphism	*N* = 170	*N* = 380		*N* = 182		*N* = 28	*N* = 121

Table 3 | (Continued)

	LDV/SOF (*N* = 1333), 8 weeks	LDV/SOF (*N* = 2615) 12 weeks	*P* value*	LDV/SOF+RBV (*N* = 1120), 12 weeks	*P* value*	OPrD (*N* = 253), 12 weeks	OPrD + RBV (*N* = 738), 12 weeks
CC	91.7 (33/36)	96.6 (86/89)		100.0 (26/26)		100.0 (3/3)	88.0 (22/25)
CT	92.1 (82/89)	94.9 (187/197)		92.6 (100/108)		100.0 (14/14)	96.9 (63/65)
TT	91.1 (41/45)	96.8 (91/94)		95.8 (46/48)		81.8 (9/11)	93.5 (29/31)

Categorical variables reported as % (*n*).

BMI, body mass index; DAA, direct-acting antiviral; LDV/SOF, ledipasvir/sofosbuvir; OPrD, ombitasvir/paritaprevir/ritonavir + dasabuvir; RBV, ribavirin; SVR, sustained virological response.

* *P* value listed for $P < 0.01$.

† Subtype 1a includes 1a mixed 1a/1b and 1 with subtype unspecified.

Table 4 | Odds ratios for sustained virological response in multivariate model for genotype 1 patients treated with ledipasvir/sofosbuvir- or ombitasvir/paritaprevir/ritonavir plus dasabuvir-based regimens

	Intention-to-treat OR (95% CI), *N* = 6525	Received 12 weeks OR (95% CI), *N* = 4720
Age <55 years (ref. 55–64)	1.37 (0.98–1.94)	1.36 (0.83–2.37)
Age ≥65 years (ref. 55–64)	1.17 (0.96–1.43)	1.26 (0.94–1.70)
Female (ref. Male)	2.23 (1.26–4.38)	2.51 (1.04–8.23)
African American (ref. Caucasian)	0.71 (0.59–0.86)***	0.86 (0.64–1.14)
Hispanic (ref. Caucasian)	0.77 (0.54–1.12)	1.00 (0.59–1.81)
Other/multiple (ref. Caucasian)	0.87 (0.62–1.23)	0.81 (0.51–1.34)
Diabetes (ref. no diabetes)	1.01 (0.83–1.22)	1.08 (0.82–1.42)
Decompensated liver disease (ref. no)	0.60 (0.41–0.90)	0.87 (0.51–1.54)
Treatment experienced (ref. naïve)	0.90 (0.73–1.11)	0.90 (0.67–1.21)
BMI <25 kg/m^2 (ref. 25–29 kg/m^2)	0.77 (0.61–0.96)	0.99 (0.69–1.44)
BMI ≥30 kg/m^2 (ref. 25–29 kg/m^2)	0.73 (0.60–0.89)**	0.66 (0.49–0.88)**
FIB-4 > 3.25 (ref. ≤3.25)	0.60 (0.49–0.72)***	0.46 (0.35–0.60)***
HCV subtype 1b (ref. 1a†)	1.38 (1.11–1.71)**	1.44 (1.04–2.02)
LDV/SOF + RBV (ref. LDV/SOF)	1.07 (0.84–1.37)	0.87 (0.64–1.19)
OPrD (ref. LDV/SOF)	1.27 (0.74–2.37)	1.68 (0.71–4.93)
OPrD+RBV (ref. LDV/SOF)	0.60 (0.48–0.76)***	1.22 (0.83–1.84)

BMI, body mass index; CI, confidence interval; LDV/SOF, ledipasvir/sofosbuvir; OPrD, ombitasvir/paritaprevir/ritonavir+dasabuvir; OR, odds ratio; RBV, ribavirin; ref., reference; SVR, sustained virological response.

† Subtype 1a includes 1a, mixed 1a/1b and 1 with subtype unspecified.

**$P < 0.01$, ***$P < 0.001$.

were observed in African Americans compared to Caucasians treated with LDV/SOF, OPrD and OPrD+RBV. In patients who received a full 12 weeks of treatment, SVR rates in African Americans were higher than in the intention-to-treat analysis and the numeric differences in SVR rates between African Americans and Caucasians were diminished.

This study included over 2300 patients with a BMI at or above 30 kg/m^2, and in the overall cohort those with high BMI were 27% less likely to achieve SVR. As one might expect, the effect of BMI on SVR was not dependent on whether the patient completed therapy and, as such, high BMI remained a negative predictor of response in those who completed a 12-week treatment course. For such patients, additional treatment options may need to be considered to optimise SVR rates.

Shorter 8 week regimens were widely used in treatment-naïve patients with baseline HCV RNA below 6 000 000 IU/mL without cirrhosis. We could only assess the use of 8 week LDV/SOF regimens in patients who completed therapy because we were unable to otherwise determine if the original provider intent was to treat for 8 or 12 weeks using the available electronic data. Although the difference in SVR rates between those who completed

8 weeks and those who completed 12 weeks was numerically small at 3.4% it was statistically significant suggesting that to optimise a patient's likelihood of SVR the 12-week duration may be preferred.

Real-world SVR rates achieved with these treatment regimens were remarkably high. The large differences between real-world effectiveness and clinical trial efficacy previously observed with HCV antiviral treatment have now been almost eliminated with the use of potent all-oral regimens. Most of the small decrement in observed effectiveness in this real-world cohort may be explained in large part by higher early discontinuation rates. Early discontinuations rates were highest in those receiving OPrD + RBV (15.2%), followed by OPrD (11.4%), LDV/SOF + RBV (8.1%) and LDV/SOF (5.3%). Clinical trials tend to have early discontinuation rates of less than 3%.[7–14] Higher early discontinuation rates had the greatest impact on SVR rates in those receiving OPrD + RBV with a nearly 10% difference in SVR rates comparing intention-to-treat (85.8%) to those who completed 12 weeks (95.5%). While we did not examine reasons for early discontinuation, adverse effects and adherence are often recognised as contributing factors. Setting appropriate expectations about potential medication side effects and continued emphasis on adherence and persistence will remain important elements in maximising treatment success. Any remaining decrement in clinical effectiveness compared to clinical trial efficacy may be explained by differences in patient populations. For example, higher BMI in our cohort was identified as a significant negative predictor of SVR.

Given the high SVR rates achieved in clinical practice even among subgroups, regimen selection will depend increasingly upon nuanced considerations. Genotype subtype, presence of cirrhosis, prior treatment regimen or presence of pre-existing resistance associated polymorphisms currently determines the need for RBV and subsequent length of treatment for certain regimens. Potential for drug interactions and comorbidities may limit use of a particular agent. Enough options presently exist to allow providers some flexibility in selecting regimens tailored to meet individual patient characteristics or needs without sacrificing effectiveness. Expectations for high SVRs have been set and now validated in real-world cohorts, thus regimen subtleties together with cost considerations and insurance coverage will be key determinants for utilisation.

While this study includes one of the largest cohorts of diverse HCV-infected patients treated in clinical practice published to date, there are limitations. Specific reasons for early discontinuation (i.e. adverse events, poor tolerability, social or behavioural issues) could not be determined from the electronic data. Duration of treatment and early treatment discontinuation rates were determined based on the cumulative dispensed days' supply which may overestimate the treatment duration as patients may have discontinued treatment even with medication in their possession. In VA, many prescriptions are filled for small quantities (e.g. 2-week supplies) which would limit the extent of the overestimation. Baseline resistance testing was not performed thus we were unable to assess the impact of this factor.

CONCLUSIONS

In this large real-world cohort of genotype 1 HCV-infected veterans treated with LDV/SOF-based or OPrD-based therapy, high SVR rates comparable to clinical trials were observed and were consistently high across all subgroups evaluated. Odds of SVR were reduced in African Americans compared to Caucasians, those receiving OPrD + RBV compared to LDV/SOF, those with advanced liver disease and those with BMI $\geq$30 kg/m^2 compared to those with lower BMI. Reduced odds of SVR for African Americans and those receiving OPrD + RBV arose in large part from early discontinuation as these predictors no longer had a significant impact on odds of SVR in those who completed a 12-week course. Advanced liver disease and higher BMI, however, persisted as significant negative predictors of SVR even when considering only those patients who completed a 12-week course. For patients with advanced liver disease and high BMI longer durations of therapy or additional treatment options may still be needed to increase SVR rates. Real-world experience from large diverse cohorts such as this is necessary to better inform and refine HCV management strategies.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. A. SVR rates by regimen for treatment-naïve genotype 1 patients receiving ledipasvir/sofosbuvir- or ombitasvir/paritaprevir/ritonavir plus dasabuvir-based regimens with durations of 12 weeks or less. B. SVR rates by regimen for treatment-experienced genotype 1 patients receiving ledipasvir/sofosbuvir- or ombitasvir/paritaprevir/ritonavir plus dasabuvir-based regimens with durations of 12 weeks or less.

AUTHORSHIP

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Author contributions: Drs Backus, Belperio, Loomis and Mole: Study concept and design. Drs Backus, Belperio, Shahoumian, Loomis and Mole: Analysis and interpretation of data; Drs Backus, Belperio: drafting of the manuscript, Drs Backus, Belperio and Mole: Critical revision of the manuscript for important intellectual content; Dr Shahoumian: Statistical analysis. This statement acknowledges that all authors approved the final version of the article, including the authorship list.

ACKNOWLEDGEMENT

Declaration of personal and financial interests: None.

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